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10/791,536	03/03/2004	Lin Shiue Lian	8964-000010/US	3361
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HARNESSE, DICKEY & PIERCE, P.L.C.			EXAMINER	
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			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/791,536

Applicant(s)

LIAN ET AL.

Examiner

Valarie Bertoglio

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 10/16/2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-11 and 16-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-11 and 16-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03/03/04 and 07/02/04 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's reply dated 10/16/2007 has been received and entered. Claims 4 and 12-15 have been cancelled. Claims 1, 11 and 23 have been amended. Claims 1-3, 5-11 and 16-24 are pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-11 and 16-24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating an ornamental fish comprising (a) generating a transgenic oviparous fish whose genome comprises one or more genes encoding a fluorescent protein operably linked to a promoter, wherein the transgene is expressed in the fish; (b) breeding the transgenic fish with a fish of the same or different species of the same genus having a phenotype or pattern that differs from the transgenic fish; and (c) screening the resulting transgenic progeny for those showing a phenotype or pattern that differs from each parent and fish made by said method, does not reasonably provide enablement for the claimed method comprising mating fish across genera or family. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is maintained, in part, for reasons of record set forth at pages 2-6 of the previous office action dated 07/03/2006.

Applicant has amended claim 1 to be limited to use of oviparous species of fish. This aspect of the rejection is withdrawn. However, the rejection is maintained on the grounds that the claims continue to encompass intergenus matings as well as interfamily matings. Claim 2 is limited to matings within the

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same family, which encompasses intergenus matings. Claim 3 requires the mating be between different families, genera or species. Applicant submits that the amendments to the claims are sufficient to limit claims to the Cyprinidae and Killifish groups for which enablement has been provided. This argument is not persuasive in light of claims 2 and 3 as well as the generic nature of claim 1, which fails to limit the method to intragenus, not intergenus, matings. Claim 11 is now limited to Cyprinidae and Killifish groups. Cyprinidae is a Family that consists of numerous Genera. Killifish appears to be a generic term encompassing fish from various Orders. Thus, the claims continue to encompass intergenus matings.

The art at the time of filing held that while interspecies matings within a genus can often occur and can also be desired, matings of distantly related species of the same genus as well as matings of fish between different genera and families are highly unpredictable as to the success of the fertilization, development, health of any progeny that do occur and fertility of offspring. Bartley *et al.* discuss the use of inter-specific hybrids in aquaculture. Hybridization between species often results in offspring that are sterile or with diminished reproductive capacity as a result of problems in gonad development and chromosome pairing (paragraph bridging columns at page 330). The results of inter-specific hybridization can lead to unexpected and undesirable results and can depend on the genetic structure of the parent fish (Abstract). While inter-specific mating of certain species is known to result in various, desirable outcomes, these combinations are not easily arrived at, as evidenced by the mating of various species of grouper (page 332, col. 2, paragraph 2). With greater the divergence between two species comes increased divergence in chromosome number, pairing and compatibility of gene products.

The specification fails to set forth, of the many families of fish, which species of fish would provide valuable hybrid offspring. For example, the specification fails to support that transgenic zebrafish could mate or produce progeny by in vitro fertilization with any other fish encompassed by the claims such as tilapia, carp or salmon.

Thus, the specification fails to provide the guidance necessary to overcome the unpredictability in the art relating to mating fish of divergent species. It would require undue experimentation to determine successful hybrid species using matings between fish of different genera.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,5-11 and 16-24 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

Claim 1 remains unclear at step (c) because as amended the claim reads “screening the transgenic progeny that exhibit for those exhibiting...”. This new phrase is unclear as written. Claims 2-3,5-11 and 16-24 depend from claim 1. Applicant has not addressed this aspect of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1,2,5-9 and 23 under 35 U.S.C. 102(b) as being anticipated by Higashijima [Developmental Biology, 1997, 192:289-299] is withdrawn in light of Applicant's amendments to the claims. Higashijima did not teach the use of flanking ITR elements.

Claims 1,2,5-9 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hsiao et al. [Developmental Dynamics, 220:323-336, April 2001].

Claims 1 and 2 are drawn to a method of making a fish comprising steps of generating a transgenic fish, breeding said fish to a second fish that has a different phenotype or pattern and screening the transgenic progenies for those exhibiting a phenotype or pattern that differs from either of the parents. Claim 1 has been amended to require flanking ITR elements in the transgene construct. Claim 5 limits claim 1 to use of a number of specific fluorescent protein encoding genes including EGFP. Claim 6 and 7 limit claim 1 to a smaller number of specific fluorescent protein encoding genes, each including GFP and EGFP. Claims 8 and 9 limit the phenotype to certain observable morphological phenotypes including body transparency and color. Claim 23 is limited to the fish made by the method of claim 1.

Hsiao taught a method of making a transgenic zebrafish with systemic fluorescence of the skeletal musculature by injecting a linearized plasmid including flanking ITRs, an α -actin promoter, a fluorescent EGFP gene and an SV40 polyA, into fertilized zebrafish embryos and allowing fluorescent embryos to develop into zebrafish (Figure 1, second construct; page 325, col. 2, paragraph 2; page 333, col. 2, paragraphs 1 and 3). Hsiao taught using leopard strain zebrafish because they have less pigmentation than the AB strain (page 333, col. 2, paragraph 4). Lack of pigmentation is important in visualizing fluorescence (see page 323, col. 2, lines 1-2). Breeding of the transgenic fish to wildtype fish meets the limitation of breeding fish with different patterns as wildtype, nontransgenic fish would not have the fluorescent pattern of the transgenic fish.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1,2,5-9 and 23 under 35 U.S.C. 103(a) as being unpatentable over Higashijima [Developmental Biology, 1997, 192:289-299] in view of Lawson and Weinstein [Developmental Biology, 248:307-318, of record] is withdrawn in light of Applicant's amendments to the claims. Neither Higashijima nor Lawson and Weinstein taught the use of flanking ITR elements.

The rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Higashijima [Developmental Biology, 1997, 192:289-299] in view of Bartley *et al* [Reviews in Fish Biology and Fisheries, 2001, 10:325-337] taken with Gong *et al* [Genetica, 111:213-225, 2001] is rendered moot by the cancellation of the claim.

The following new rejections are necessitated by claim amendment.

1) Claims 1,2,5-9 and 23 are rejected under 35 U.S.C. 103(a) as being anticipated by Hsiao *et al*. [Developmental Dynamics, 220:323-336, April 2001] in view of Lawson and Weinstein [Developmental Biology, 248:307-318, of record].

As set forth above in the rejection under 35 USC 102(b), breeding of the transgenic fish to wildtype fish meets the limitation of breeding fish with different patterns as wildtype, nontransgenic fish would not have the fluorescent pattern of the transgenic fish. However, in the alternative, the claims can be interpreted as crossing to a fish have a phenotype that does not differ as a result of the claimed transgene.

Thus, as set forth above, Hsiao taught a method of making a transgenic zebrafish with systemic fluorescence of the skeletal musculature by injecting a linearized plasmid including flanking ITRs, an α -actin promoter, a fluorescent EGFP gene and an SV40 polyA, into fertilized zebrafish embryos and allowing fluorescent embryos to develop into zebrafish (Figure 1, second construct; page 325, col. 2,

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paragraph 2; page 333, col. 2, paragraphs 1 and 3). Hsiao taught using leopard strain zebrafish because they have less pigmentation than the AB strain (page 333, col. 2, paragraph 4). Lack of pigmentation is important in visualizing fluorescence (see page 323, col. 2, lines 1-2). Hsiao did not teach mating the claimed transgenic, fluorescent fish to a fish of different pattern other than nontransgenic fish that differ only in the phenotype effected by the transgene.

However, Lawson and Weinstein taught generating a transgenic GFP expressing zebrafish using one strain of fish (EK) and mating the transgene from the EK into an unpigmented albino mutant of the same species, resulting in a transgenic GFP, albino mutant. For example, see Figure 5 and legend. Albino mutants have an altered body transparent level as a result of a loss of pigmentation.

It would have been obvious at the time the application was filed to combine the teachings of Hsiao in making a transgenic fish exhibiting stable and reproducible fluorescent reporter gene expression with those of Lawson and Weinstein to mate the transgene of Hsiao into an albino mutant fish. One of skill in the art would have been so motivated to obtain a fish exhibiting a fluorescent pattern that is not obscured by the natural pigment pattern of the fish.

One would have a reasonable expectation of success in carrying out the combination because albino mutant zebrafish will readily mate with other zebrafish.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 2 and 3 are rejected under 35 USC 103(a) as being unpatentable over Hsiao (et al. [Developmental Dynamics, 220:323-336, April 2001] in view of Bartley *et al* [Reviews in Fish Biology and Fisheries, 2001, 10:325-337, of record] taken with Gong et al [Genetica, 111:213-225, 2001, of record]).

Claims 2 and 3 encompass both interspecific and intraspecific matings. Inter-genus and intra-genus matings are not enabled as set forth above.

Hsiao taught a method of making a transgenic zebrafish with systemic fluorescence of the skeletal musculature by injecting a linearized plasmid including flanking ITRs, an α -actin promoter, a fluorescent EGFP gene and an SV40 polyA, into fertilized zebrafish embryos and allowing fluorescent embryos to develop into zebrafish (Figure 1, second construct; page 325, col. 2, paragraph 2; page 333, col. 2, paragraphs 1 and 3). Hsiao taught using leopard strain zebrafish because they have less pigmentation than the AB strain (page 333, col. 2, paragraph 4). Lack of pigmentation is important in visualizing fluorescence (see page 323, col. 2, lines 1-2). Hsiao did not teach interspecific breeding.

However, Bartley *et al.* taught that there are many different species of fish that can interbreed to form hybrid species and that hybrid species often can lead to more desirable traits including a variety of traits that make fish more profitable to raise (see paragraph bridging columns at page 326) or that result in alterations in morphology (phenotype).

Furthermore, Gong *et al.* taught the use of transgenic fluorescent protein expressing fish as having ornamental value (see page 222).

It would have been obvious at the time the application was filed to combine the teachings of Hsiao in making a transgenic fish exhibiting stable and reproducible fluorescent reporter gene expression with those of Bartley to mate the transgene of Hsiao into a fish of different species to create fish with a combination of parental traits. One of skill in the art would have been so motivated to obtain such a fish because Gong *et al.* pointed out the use of fluorescent fish as having ornamental value and interspecies crosses would supply an already integrated and expressed transgene to fish of different morphologies.

One would have a reasonable expectation of success in carrying out the combination because interspecies mating of certain closely related fish was known and routine in the art.

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Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The double patenting warning is withdrawn in light of Applicant's cancellation of claim 4.

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Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
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